



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Dasch *et al.*

Appl. No.: 10/681,571

Filed: October 8, 2003

For: **Method of Modifying the Release
Profile of Sustained Release
Compositions**

Art Unit: 1616

Examiner: E. Webman

Atty. Docket: 00166.2040-US01

**Second Declaration of Elliot W. Ehrich, M.D.
Under 37 C.F.R. § 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Elliot W. Ehrich, M.D., hereby declare and state as follows.

1. I have a Bachelor's degree in Biochemistry, and a Doctorate degree in Medicine and certification by the American Board of Internal Medicine. I have over fourteen years experience in the biotechnology and pharmaceutical industries. I am currently employed by Alkermes, Inc. ("Alkermes") as Senior Vice President, Research and Development, Chief Medical Officer. I have been employed by Alkermes or their predecessor in business for more than seven years.

2. This is my second declaration relating to the above-captioned application. My first declaration is dated July 2, 2007 (referred to herein as the "First Ehrich Declaration"), the contents of which are incorporated herein by reference.

3. The above-captioned U.S. Patent Application No. 10/681,571 ("the '571 application") is owned by Alkermes Controlled Therapeutics Inc., a subsidiary of Alkermes. I

have read and understood the '571 application. I am familiar with the technology of the invention disclosed in the '571 application through my education and my work at Alkermes.

4. I have read and understood the Final Office Action dated September 25, 2007 that has issued in the '571 application. I have also read and understood U.S. Patent No. 5,707,644 ("the '644 patent") and U.S. Patent No. 5,610,159 ("the '159 patent") that are referred to in the Final Office Action. The '159 patent is directed to a class of morpholine derivatives which are useful as tachykinin antagonists. The tachykinins are a group of naturally occurring peptides that are found throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems. '159 Patent, Col. 1, Lines 1-12.

5. Page 2 of the Final Office Action states that "[I]t is well known that inflammation is associated with diabetes (See Moseley et al [the '159 patent], column 13 lines 45-49)." The text of column 13, lines 15-51 of the '159 patent is reproduced below:

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis, headache and especially migraine.

6. Based on my years of clinical experience and education, I respectfully disagree with the Examiner's conclusion from the text of column 13, lines 15-51 of the '159 patent that it is "well known that inflammation is associated with diabetes." Not only is the Examiner's conclusion contrary to my clinical experience, but the Examiner appears to be making a false

linkage between “and/or inflammation” and “diabetic and chemotherapy-induced neuropathy.” Based on my years of clinical experience and education, I submit that one skilled in the art of sustained release compositions and their use *in vivo* would understand the text of column 13, lines 15-51 of the ‘159 patent to be stating that the compounds of the ‘159 patent are useful for the treatment of diabetes-induced neuropathy (an abnormal and usually degenerative state of the nervous system or nerves). I submit that one skilled in the art of sustained release compositions and their use *in vivo* would not understand the text of column 13, lines 15-51 of the ‘159 patent to be stating that inflammation is associated with diabetes. The reading of the text at column 13, lines 15-51 that the compounds of the ‘159 patent are useful for the treatment of diabetes-induced neuropathy is consistent not only with the grammar and natural reading of the text, but also with my clinical experience and knowledge relating to diabetes. The reading of the text at column 13, lines 15-51 of the ‘159 patent that “inflammation is associated with diabetes” is not consistent with the grammar and natural reading of the text, nor with my clinical experience and knowledge relating to diabetes.

7. The ‘644 patent is directed to a drug delivery composition for intranasal delivery that includes a plurality of bioadhesive microspheres and a systemically active drug. One of the listed drugs is insulin. ‘644 Patent, Col. 2, Lines 22-32; Col. 7, Lines 26-27; Abstract. The microsphere composition of the ‘644 patent may be used with other drugs, including hydrocortisone and triamcinolone acetonide. ‘644 Patent, Col. 7, Lines 65-66. However, the ‘644 patent makes no mention of exendin.

8. Page 2 of the Final Office Action states that “[I]t would have been obvious to one of ordinary skill in the art to deliver exendin in the composition of Illum [the ‘644 patent]

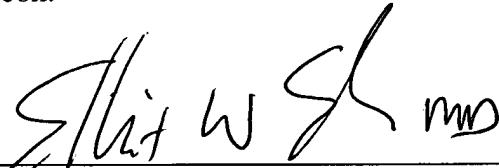
containing insulin to achieve the beneficial effect of an anti-diabetic agent in view of Eng.” The First Ehrich Declaration addressed in detail why the addition of exendin to an insulin formulation such as that disclosed in the ‘644 patent would not achieve a beneficial effect of an anti-diabetic agent.

9. Page 2 of the Final Office Action also states that “it would be further obvious to one of ordinary skill to include triamcinolone acetonide in the obvious composition to achieve the beneficial effect of treating inflammation associated with diabetes.” As discussed above in paragraphs 5-6, I respectfully disagree with the Examiner’s conclusion that inflammation is associated with diabetes because this conclusion is not consistent with the ‘159 patent nor with my years of clinical experience and education. For at least the following reasons, I respectfully disagree with the Examiner’s position that “it would be further obvious to one of ordinary skill to include triamcinolone acetonide” in an insulin or exendin composition for the purpose of “treating inflammation associated with diabetes.”

10. Triamcinolone acetonide and hydrocortisone are both corticosteroids. The administration of steroids, including corticosteroids, makes it more difficult to maintain glucose control. Maintaining glucose control is critical for a patient with diabetes. A clinician treating a diabetes patient would avoid the administration of a steroid because that would make the glucose control more difficult to maintain. Inflammation is not a recognized consequence of diabetes. To the extent a diabetes patient required treatment for inflammation due to some other cause, a clinician would avoid a steroidal approach to avoid the difficulty with respect to glucose control associated with steroids.

11. The invention of the '571 application is based upon the unexpected discovery that the release profile of a biologically active labile agent from a sustained release composition can be modified when a corticosteroid is co-administered. '571 Application, Page 2, Lines 13-18. In the claimed sustained release composition of the '571 application, the corticosteroid is present only in an amount sufficient to modify the release profile of the labile agent from the biocompatible polymer and provide increased bioavailability of the labile agent. Such an amount is not sufficient for "treating inflammation associated with diabetes" nor is it sufficient for adversely affecting glucose control. The corticosteroid is present in an amount that allows for natural diffusion and degradation of the polymer, minimizing or eliminating polymer degradation caused by foreign body reactions within a tissue, such as hydrolyzation by macrophage enzymes, thereby allowing for an extended period of release of at least about two weeks. The foreign body reactions within a tissue result from administration by injection or implantation, such as subcutaneously, intramuscularly, intraperitoneally, intracranially, and intradermally. One skilled in the art of sustained release compositions and their use *in vivo* would not expect a similar effect by administering to mucosal membranes (*e.g.*, intranasally) because foreign body reactions do not occur on the surface of mucosal membranes.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-captioned patent application or any patent issued thereon.



Elliot W. Ehrich, M.D.

Date: 1/17/08